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Role of the NF-κB Pathway in the Pathogenesis of Human Disease States

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Abstract: The NF-κB family consists of a group of inducible transcription factors which regulate immune and inflammatory responses and protect cells from undergoing apoptosis in response to cellular stress. A number of signal transduction cascades can activate the NF-κB pathway to result in the translocation of the NF-κB proteins from the cytoplasm to the nucleus where they activate the expression of specific cellular genes. In this review, we discuss cellular genes which are regulated by NF-κB and disease states which are associated with constitutive activation of the NF-κB pathway. Strategies to prevent prolonged activation of the NF-κB pathway are also discussed.

INTRODUCTION

NF-κB plays a role in regulating the host inflammatory and immune response and in preventing cellular apoptosis in response to cellular stresses [1-4]. The NF-κB proteins increase the expression of specific cellular genes including cytokines and chemokines, the major histocompatibility complex (MHC), and receptors required for neutrophil adhesion and migration [1-5]. Cytokines including interleukin 1β (IL-1β) and tumor necrosis factor α (TNFα) can also directly activate the NF-κB pathway. This can result in a positive auto-regulatory loop that contributes to the amplification of the inflammatory response and the persistence of chronic inflammation at local sites. In addition, NF-κB can stimulate the expression of enzymes including the inducible form of nitric oxide synthase (iNOS) that generates nitrous oxide (NO) and the inducible cyclo-oxygenase (COX-2) that generates prostanoids [6, 7]. These metabolites contribute to the pathogenesis of the inflammatory process. Finally, NF-κB is involved in the control of the immune response by regulating B-lymphocyte function [8] and cytokine-induced proliferation of T-lymphocytes [9]. Thus the NF-κB proteins are important in activating the expression of multiple genes that regulate the immune and the inflammatory response.

NF-κB also regulates the expression of genes involved in the control of the cellular proliferation and apoptosis [10]. These include the cellular inhibitors of apoptosis (cIAP1, cIAP2, and IXAP) [11, 12], the TNF receptor associated factors (TRAF1 and TRAF2) [12], the bcl-2 homologue A1/Bfl-1, and IEX-IL [13]. The anti-apoptotic proteins TRAF1, TRAF2, IAP-1, and IAP-2 protect cells from TNFα-induced apoptosis by inhibiting the activation of caspase-8, a protease involved in inducing the apoptotic process [12]. The bcl-2 family of proteins are key regulators of apoptosis, possessing both anti-apoptotic (Bcl-2, Bcl-XL, A1/Bfl-1, etc) and pro-apoptotic (Bad, Bax, Bcl-XS) properties [14]. NF-κB induces the expression of a member of the bcl-2 family, A1/Bf1-1 [15] and this factor prevents apoptosis in B-lymphocytes. Treatment of cells with the chemotherapeutic agent etoposide also increases NF-κB activity and results in the induction of A1/Bfl-1 which prevents cytochrome c release from mitochondria [16]. Thus NF-κB activation can reduce apoptosis in response to a variety of stimuli that induce cell death.

Mechanisms Regulating NF-κB Activation

The NF-κB proteins share a 300 amino acid domain which is designated the Rel homology domain [1-4] which mediates the DNA binding, dimerization, and nuclear transport of the NF-κB proteins. NF-κB family members including c-Rel, Rel B and p65 also contain a transactivation domain while other members including p50 and p52, possess DNA binding and dimerization domains but not strong transactivation domains [17].

In most cells, the NF-κB proteins are localized in the cytoplasm bound to a family of inhibitor proteins known as IκB (IκBα, IκBβ, IκBε) [1-4]. The IκB proteins block the NF-κB nuclear localization signal and thus help to maintain the cytoplasmic localization of the NF-κB proteins. A variety of

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stimuli including tumor necrosis factor α (TNFα) and interleukin-1 (IL-1), phorbol esters, lipopolysaccharide (LPS), viral infection, the HTLV-I transforming protein Tax and UV radiation, lead to the degradation of IκB and the nuclear translocation of NF-κB [2].

The phosphorylation of the IκB proteins is a key step involved in the regulation of the NF-κB pathway. The phosphorylation of the IκB proteins is regulated by IκB kinases (IKK) whose activity is strongly induced by agents that stimulate the NF-κB pathway such as TNFα and IL-1β [18, 19]. The IKK complex contains two kinase subunits, IKKα and IKKβ, and the associated modulatory protein, IKKγ or NEMO [20]. These kinases have 52% amino acid identity and a similar structural organization which include kinase, leucine zipper, and helix-loop-helix domains. IKKα and IKKβ can form both heterodimers and homodimers via interactions mediated by their leucine zipper domains. Biochemical analysis and gene disruption studies of the IKK genes in mice indicate that IKKβ is the critical kinase involved in activating the NF-κB pathway while IKKα likely plays an accessory role although both IKKα and IKKβ are essential genes for mouse viability [20]. IKKγ/NEMO, which itself does not possess kinase activity, is also critical for the activation of the NF-κB pathway in response to a variety of different signals.

Treatment of cells by agents that stimulate the NF-κB pathway, leads to the phosphorylation of specific serine residues in the activation loop of each IKK subunit [21]. IKK then phosphorylates the IκB proteins on two closely spaced serine residues in the amino terminus to result in their ubiquitination and subsequent degradation by the 26S proteasome [18, 19, 22]. This process leads to NF-κB translocation to the nucleus where these proteins bind to specific elements in the promoter regions of target genes to activate gene expression.

NF-κB transcriptional activation can also be regulated by phosphorylation of the Rel family member p65. The p65 subunit contains the Rel homology domain in its amino terminus and two transactivation domains in its carboxy-terminus [23]. Phosphorylation of serine residue 276 in p65 by protein kinase A facilitates its interaction with the coactivator protein CBP to result in enhanced p65 transcriptional activity. TNFα-treatment of cells can also induce p65 phosphorylation, but this phosphorylation occurs on serine residue 529 to also result in enhanced p65 transactivation properties [24]. The IKKs can directly phosphorylate residues in the transactivation domain of p65. For example, both endogenous and recombinant IKK can phosphorylate serine residue 536 in the p65 transactivation domain [25]. In addition, the IKKs can contribute either directly or indirectly with the ability of the PI-3 inducible kinase AKT to stimulate p65 transactivation [26]. Finally, activation of IKK kinase activity can also result in phosphorylation of the NF-κB precursor p105 leading to enhanced processing and nuclear translocation of p50 [27]. These results indicate that the phosphorylation of p65 and p105 are also critical determinants involved in activation of the NF-κB pathway.

In addition to regulation of IKK activity, the regulation of IκB ubiquitination and its subsequent degradation by the proteasome is required for NF-κB activation [19, 22]. The regulation of the nuclear translocation of different members of the NF-κB family is also involved in the ability of the NF-κB proteins to activate gene expression. Given the important role of the NF-κB pathway in regulating inflammation and cellular growth, it is not surprising that alterations of the NF-κB pathway are involved in the pathogenesis of a variety of disease states. A diagram of the steps involved in the regulation of the NF-κB pathway is shown in Fig. (1).

Role of NF-κB in Diseases Mediated by the Inflammatory Response

Studies indicate that activation of the NF-κB pathway is involved in the pathogenesis of chronic inflammatory diseases, such as asthma, rheumatoid arthritis and inflammatory bowel disease. In addition, altered NF-κB regulation may be involved in other diseases such as atherosclerosis, Alzheimer's disease and diabetes melitus in which the inflammatory response is at least partially involved.

Asthma

NF-κB activation is likely an important contributor to the pathogenesis of asthma which is characterized by the infiltration of inflammatory cells in lung tissue and the corresponding increase in cytokine production [28]. Biopsies of patients with mild asthma reveal increases in the nuclear levels of NF-κB in the bronchial epithelium [29]. NF-κB activates the expression of the chemokine RANTES which is produced by pulmonary macrophages and respiratory epithelial cells and is known to play a role in the recruitment of monocytes, T-lymphocytes and eosinophils to inflammatory sites in the lung [30]. In experimental animals, allergen exposure activates NF-κB in pulmonary macrophages with concomitant expression of iNOS and the generation of NO [31]. Multiple physiologic functions in the lung are regulated by NO including smooth-muscle relaxation, neurotransmission, vascular tone and host defense. Stimulation of iNOS expression resulting from NF-κB activation may underlie the increased amounts of NO seen in the exhaled air of asthmatic patients [32]. Thus inhibition of the NF-κB pathway may be a useful potential target for agents with utility in the treatment of asthma.

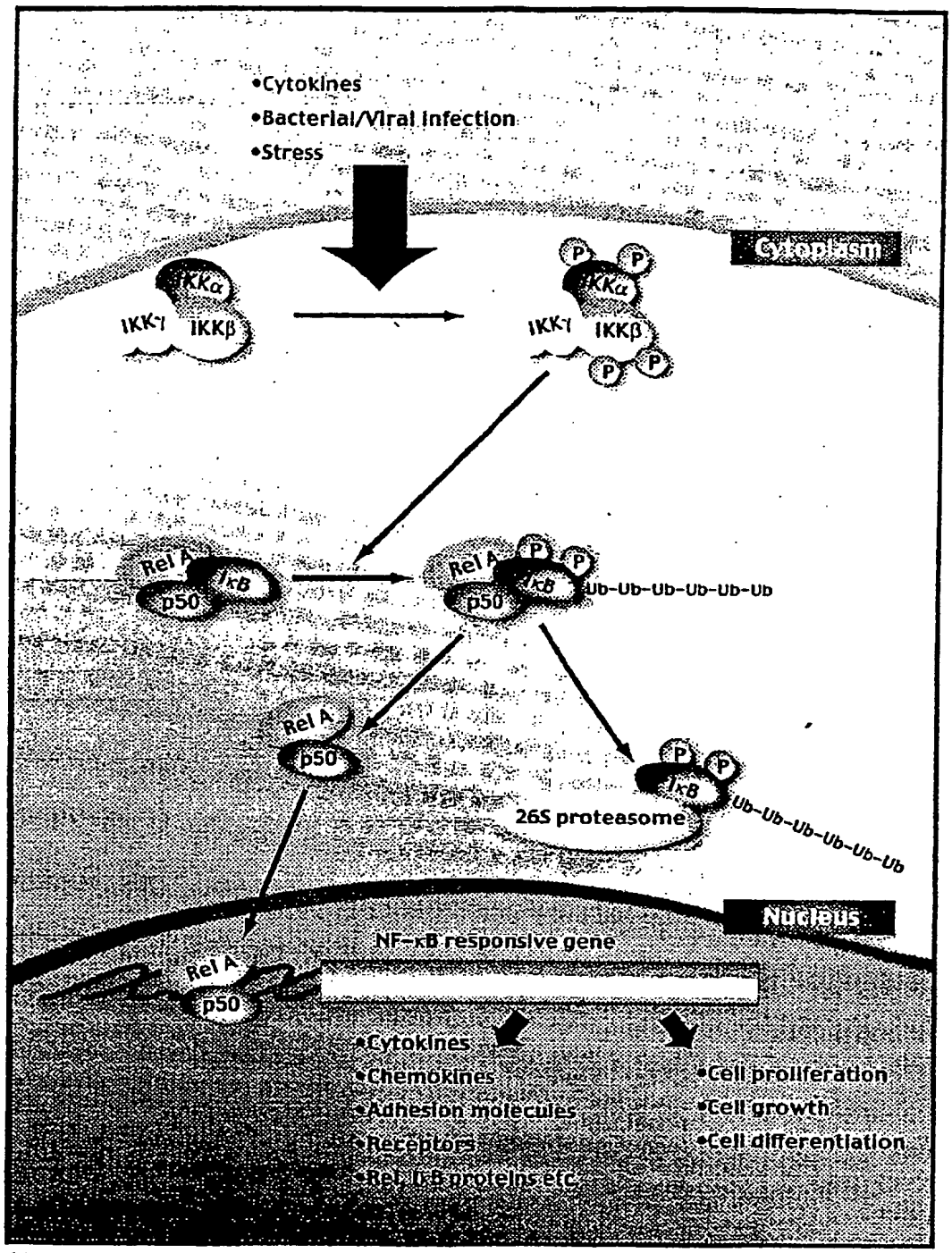

Figure 1. Regulation of the NF-κB pathway. A schematic illustrating the different processes required to activate the NF-κB pathway is shown.

Rheumatoid Arthritis

The activation of the NF-κB pathway also likely plays a role in the pathogenesis of rheumatoid arthritis. Cytokines, in particular TNFα, are elevated in the synovial fluid of patients with rheumatoid arthritis. The overexpression of these cytokines may contribute to the chronic inflammatory changes and synovial hyperplasia seen in the joints of patients with rheumatoid arthritis [33]. Overproduction of TNFα may be a major factor in the pathogenesis of rheumatoid arthritis as

suggested by the success of clinical trials utilizing TNFα antibody in the treatment of patients with rheumatoid arthritis [34]. The majority of TNFα is produced by macrophages which are enriched in the synovium of patients with rheumatoid arthritis. The production of TNFα by these macrophages can be inhibited by the suppression of NF-κB [35]. NF-κB levels are elevated in both synovial biopsy specimens obtained from patients with rheumatoid arthritis [36, 37] and animal models of this disease [38]. Suppression of NF-κB activity enhances the apoptosis of synovial cells suggesting that elevated levels of NF-κB may be an important factor contributing to synovial hyperproliferation [38]. Thus, therapies that prevent NF-κB activation have the potential to prevent the hyperplasia of the synovium and reduce the inflammatory response in patients with rheumatoid arthritis.

Inflammatory Bowel Disease

Increases in the production of pro-inflammatory cytokines may be involved in the pathogenesis of inflammatory bowel diseases, including Crohn's disease and ulcerative colitis [39]. Increased nuclear levels of NF-κB are seen in mucosal biopsy specimens from patients with Crohn's disease and ulcerative colitis, suggesting that stimulation of this pathway may be involved in the inflammatory response associated with these diseases [40]. Inhibiting NF-κB activity can block the gene expression of iNOS, IL-1β and IL-8 genes in human intestinal epithelial cells in response to treatment with either IL-1β, TNFα or PMA [41]. Treatment of patients with inflammatory bowel diseases with steroids results in decreased NF-κB activity in biopsy specimens and reduced clinical symptoms [42]. In an animal model of colitis, local administration of p65 antisense oligonucleotides can reverse the chronic inflammatory changes which are associated with increases in NF-κB activity [43]. Thus NF-κB likely plays a critical role in the pathogenesis of inflammatory bowel disease.

Atherosclerosis

Atherosclerosis is triggered by chronic injury to the endothelium and smooth muscle of blood vessels [44]. A number of different cytokines and chemokines released from endothelial cells, smooth muscle, macrophages and lymphocytes are involved in this chronic inflammatory and fibroproliferative process [44]. Activation of the NF-κB pathway plays an important role in the evolution of artherosclerosis. Using immunofluorescence and immunohistochemical techniques with a monoclonal antibody that recognizes the Rel A subunit not bound to the inhibitory protein IκBα, NF-κB activation has been demonstrated in smooth muscle cells, macrophages and endothelial cells in atherosclerotic lesions obtained from autopsy [45]. One of the substances that triggers or modulates atherosclerosis is oxidized low-density lipoproteins (oxLDLs), which deliver cholesterol and other lipids to vascular sites. Several studies show that NF-κB activity is differentially regulated by oxLDLs based on the level of oxidation of the LDLs and the type of cells in the vessel wall and their state of activation [46-48]. A short exposure to oxLDL activates NF-κB in resting monocytes and is accompanied by increases in the expression of the NF-κB inducible gene IL-8 [45]. However, prolonged exposure to oxLDL prevents subsequent NF-κB activation in monocytes [46], vascular smooth-muscle cells [46] and T-lymphocytes [48]. Thus transient activation of the NF-κB pathway by oxLDL may contribute to the development of chronic, low levels of inflammation at certain stages during the development of atherosclerosis.

Alzheimer's Disease

Alzheimer's disease is characterized by two pathological hallmarks. The first is intracellular neurofibrillary tangles which consist mostly of the paired helical filament tau and are associated with the formation of advanced glycation end products (AGEs). The second is the formation of extracellular aggregates of β-amyloid (AB) protein which forms neuritic plaques [49]. Both of these processes lead to NF-κB activation. For example, components of neurofibrillary tangles have been reported to generate reactive oxygen intermediates leading to NF-κB nuclear translocation and the activation of cytokines including IL-6 which are observed in neurons in patients with Alzheimer's disease [50]. Neuritic plaques in Alzheimer's disease are densely surrounded by reactive astrocytes which produce inflammatory cytokines including IL-1β and TNFα in addition to iNOS which generate free radicals such as NO that can be neurotoxic [51, 52]. Low levels of β–amyloid in these neuritic plaques in conjunction with inflammatory cytokines can activate the NF-κB pathway [52, 53]. These results suggest that both advanced glycation end products and β-amyloid activate the NF-κB pathway to increase the level of inflammatory cytokines that are in part responsible for the neurotoxicity seen in Alzheimer's disease. Furthermore, NF-κB immunoreactivity is found predominantly in and around early neuritic plaque types in Alzheimer's disease, whereas mature plaque types show vastly reduced NF-κB activity [54]. Thus NF-κB activation may play an important role in the initiation of neuritic plaques and neuronal apoptosis during the early phases Alzheimer's disease.

Diabetes

Increased generation of reactive oxygen species (ROS) which induces the NF-κB pathway is considered to be a factor in the development and pathogenesis of diabetes melitus. The peripheral

blood mononuclear cells isolated from patients with diabetic nephropathy show high levels of NF-κB binding activity and strong immunohistological staining for activated NF-κB. Administration of the antioxidant thioctic acid (α-lipoic acid) to these patients results in marked decreases in NF-κB activity in mononuclear cells [55]. The generation of ROS which can be triggered by multiple factors has been implicated in pancreatic beta cell death, which is a hallmark of insulin-dependent diabetes mellitus (IDDM) [56]. In animal models of IDDM, a role for the generation of ROS and induction of NF-κB activity has been demonstrated [57, 58]. For example, the injection of alloxan, which is known to produce ROS during its metabolism and induces pancreatic beta cell damage, increases NF-κB binding properties in pancreatic nuclear extract [57]. Dietary supplementation of antioxidants, such as the glutathione precursor N-acetyl-cysteine, inhibited alloxan-induced NF-κB activation and reduced hyperglycemia in alloxan-induced diabetes [57]. Another diabetogenic agent, steptozotocin (STZ), can also increase NF-κB activity in pancreatic islet cells [58]. Pretreatment of α-phenyl-tert-butylnitrone (PBN), a commonly used spin trapping agent, is capable of preventing NF-κB activation and reducing the severity of hyperglycemia induced by alloxan and STZ [58]. These findings suggest that antioxidant therapies which prevent the activation of the NF-κB pathway may be of therapeutic importance in preventing the development of diabetes melitus.

Incontinentia Pigmenti

Familial incontinentia pigmenti (IP), an X-linked dominant disorder, has recently been shown to be due to mutations in the IKKγ/NEMO gene which plays a key role in regulating IκB kinase activity [59]. Affected males with this syndrome die in utero while heterozygous females are characterized by unusual patterns of skin pigmentation with variable abnormalities of the skin, hair, nails, teeth and eyes [60]. Biopsies and cells from affected area of IP patients demonstrate deficient IKKγ/NEMO expression [59]. Murine knockout studies confirmed that disruption of the X-linked IKKγ/NEMO gene is embryonic lethal in heterozygous males while females develop a unique dermatopathy, including massive granulocyte infiltration and hyperproliferation and increased apoptosis of keratinocytes [61, 62]. IKKγ/NEMO deficient murine embryo fibroblasts exhibit decreased NF-κB activation in response to proinflammatory cytokines and showed increased sensitivity to TNFα-induced apoptosis [61-63]. In mice, the deficiency of IKKγ/NEMO also interferes with the generation of lymphocytes and results in a small thymus with destruction of cortical lymphocytes as the result of increased apoptosis [61, 62]. Thus data from both mice and humans suggest that the IKKγ/NEMO gene is an essential component required for NF-κB activation [64, 65] and its absence results in a novel genetic disorder.

Constitutive Activation of the NF-κB Pathway in Cancer

Alterations in the regulation of the NF-κB pathway have been demonstrated to play a role in the pathogenesis of some human cancers. A variety of different abnormalities in the regulation of the NF-κB pathway are frequently seen in human malignancies [66]. Most of these changes are likely due to alterations in regulatory proteins that activate signaling pathways that result in the activation of the NF-κB pathway and the constitutive presence of NF-κB in the nucleus. In addition, mutations that inactivate the IκB proteins and amplification and rearrangements of genes encoding NF-κB family members are abnormalities in the NF-κB pathway that are seen in some tumors.

Leukemias and Lymphomas

Activation of the NF-κB pathway leading to constitutive nuclear expression of NF-κB occurs in many cases of leukemia, lymphoma and solid tumors [66]. One of the best studied examples of how the constitutive activation of the NF-κB pathway is involved in the pathogenesis of malignancy is Hodgkin's disease [67-71]. Reed-Sternberg cells, which are the malignant cells involved in the pathogenesis of Hodgkin's disease, frequently exhibit constitutive nuclear levels of NF-κB [67, 68, 71]. The activation of NF-κB in these cells is likely mediated by up-regulation of specific signal transduction pathways. In a portion of Hodgkin's disease cases, which are Epstein-Barr virus (EBV) positive, the EBV-encoded protein LMP-1 can constitutively activate the NF-κB pathway [70]. The activation of the NF-κB pathway in both EBV positive and negative Hodgkin's disease leads to enhanced expression of the cytokines GM-CSF, IL-6, TNFα, and IL-13 which can stimulate the growth of Reed-Sternberg cells in an autocrine manner [72]. In addition to stimulation of signaling pathways that lead to NF-κB activation, mutations that inactive the IκBα gene and lead to the constitutive activation of the NF-κB pathway are also found in a subset of Reed-Sternberg cells [69, 70]. Persistent activation of the NF-κB pathway is also seen in more than 90% of patients with acute lymphoblastic leukemia [73] and in all cases of adult T-cell leukemia induced by the human T-cell leukemia virus type 1 [74]. Thus a number of different mechanisms are involved in NF-κB activation in Hodgkin's disease and leukemias.

Constitutive NF-κB Activation in Solid Tumors

Persistent activation of the NF-κB pathway is also seen in a variety of solid tumors including breast

[75-77], ovarian [75, 78], colon [75], pancreatic [79] prostate [80]. In breast cancer, the constitutive activation of the NF-κB pathway is frequently seen in primary breast cancer leading to enhanced nuclear binding of different NF-κB subunits and increased expression of NF-κB inducible genes [76, 77, 81]. The activation of NF-κB in breast cancer has been reported to correlate with hormone-independent growth and a more aggressive clinical course [76]. Inhibition of NF-κB activity in breast cancer cell lines can lead to apoptosis [77]. Constitutive NF-κB activation is also seen in primary prostate cancers [80, 82] and again inhibition of NF-κB activity in prostate cancer cell lines can lead to apoptosis [83]. The activation of the NF-κB pathway in a variety of solid tumors may be mediated by mutations in specific regulatory proteins such as the oncogene *ras* which is an upstream activator of the NF-κB pathway [84].

Genetic Changes in the NF-κB Pathway in Cancer

The NF-κB pathway can also be activated by chromosomal changes. The c-Rel gene is frequently amplified in large cell lymphomas and is associated with advanced disease stage [85, 86]. Portions of the NF-κB2 gene which encodes p100 and p52 are deleted in some lymphomas and leukemias leading to constitutive nuclear expression and increased DNA binding properties of this NF-κB subunit [87]. Finally, constitutive activation of the NF-κB pathway can lead to resistance to tumor cell killing by chemotherapy and radiation therapy [88]. The mechanism of this resistance is frequently due to enhanced expression of anti-apoptotic genes. However, NF-κB overexpression can also lead to enhanced expression of the multi-drug resistance gene product (MDR) which contributes to resistance to chemotherapy-induced cell killing [89]. The MDR proteins, which function as energy-dependent efflux pumps that prevent intracellular cytotoxic drug accumulation, are highly expressed in many tumors. NF-κB has been implicated in the activation of MDR gene expression [89]. These results provide another potential mechanism by which NF-κB activity can cause resistance to different anti-cancer agents. Thus, constitutive NF-κB activation is important in the pathogenesis of a number of human diseases including cancer.

Inhibitors of the NF-κB Pathway

A variety of different ways to inhibit the NF-κB pathway have been described which can potentially alter disease states that are due to constitutive NF-κB activation. These include degradation resistant IκB mutants delivered by adenoviral expression vectors, glucocorticoids, non-steroidal anti-inflammatory drugs including aspirin and sulindac, and proteasome inhibitors. The signal-induced phosphorylation of IκBα and its degradation is required for NF-κB activation [18, 22, 88, 90, 91]. An IκB mutant in which its phosphorylation is prevented by the substitution of alanine for serine residues at positions 32 and 36 is resistant to cytokine-induced degradation. This IκBα mutant or super-repressor has a dominant negative phenotype by sequestering NF-κB in the cytoplasm to prevent activation of this pathway. The expression of the IκB super-repressor enhances the sensitivity of cells to TNFα-induced apoptosis [88, 91, 92] and to cell death by treatment with either ionizing radiation or chemotherapeutic agents [88]. All of these agents stimulate the NF-κB pathway and thus induce factors that prevent apoptosis. However, blocking activation of the NF-κB pathway by the IκB super-repressor prevents activation of these factors and thus enhances the pro-apoptotic properties of TNFα reduction and chemotherapy.

Glucocorticoids, such as dexamethasone and prednisone, have potent anti-inflammatory and immunosuppressive properties. Glucocorticoids induce the gene expression of the IκBα gene to result in enhanced cytosolic retention of NF-κB [93, 94]. The rapid degradation of IκBα protein seen in response to either TNFα or phorbol ester treatment of cells can thus be compensated for by dexamethasone-induced synthesis of IκBα. Thus NF-κB is maintained in an inactive cytoplasmic complex so that the expression of genes involved in the pathogenesis of the immune response is reduced. However, glucocorticoids can also down-regulate NF-κB directed gene expression by other mechanisms. For example, competition between NF-κB and the glucocorticoid receptor for limiting amounts of the coactivators, CBP (CREB-binding protein) and SRC-1 (steroid receptor coactivator-1) may also be involved in glucocorticoid mediated inhibition of NF-κB [95]. It is likely that glucocorticoids exert their effects at multiple steps in the NF-κB pathway to prevent its activation.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have anti-inflammatory properties [96], and also prevent the development of colon cancer [96, 97]. NSAIDs inhibit cyclo-oxygenase activity to prevent prostaglandin synthesis [98], although additional mechanisms involved in the actions of these agents have been reported [99-102]. Aspirin and sodium salicylate can inhibit NF-κB activation. At concentrations measured in the serum of patients treated with these agents for chronic inflammatory conditions, both aspirin and salicylate inhibit activation of the NF-κB pathway [99-102]. The inhibitory effects of aspirin and sodium salicylate were shown to result from the specific inhibition of IKKβ kinase activity by reducing its ability to bind ATP [101]. Thus IKKβ phosphorylation of IκBα is markedly reduced preventing its degradation by the proteasome and activation of the NF-κB pathway. Indomethacin which can alone inhibit cyclo-

oxygenase activity and has potent anti-inflammatory responses does not prevent activation of the NF-κB pathway [99-102]. The effects of aspirin and sodium salicylate on inhibiting the NF-κB pathway appear to be independent of their ability to block cyclo-oxygenases.

Sulindac is a non-steroidal anti-inflammatory agent that is structurally that is converted by bacteria in the colon to the metabolites sulindac sulfide and sulindac sulfone [103, 104]. Sulindac sulfide, but not sulindac sulfone, blocks prostaglandin synthesis by non-selective inhibition of cyclo-oxygenase 1 and 2 [105]. Although the anti-inflammatory and growth inhibitory properties of sulindac and its metabolites are due at least in large part to their inhibitory effect on cyclo-oxygenase, these agents also inhibit the activation of the NF-κB pathway by inhibiting IKK kinase activity [102]. Both sulindac and aspirin can induce apoptosis in HCT-15 cells, a colon carcinoma cell line, that is defective in the generation of prostaglandins [102]. Thus inhibition of the NF-κB pathway may be involved in the anti-inflammatory and the growth inhibitory properties of certain NSAIDs.

Inhibitors of proteasome function reduce the degradation of IκB in response to cytokine-induced phosphorylation and ubiquitination and thus prevent activation of the NF-κB pathway [106]. Several groups of agents including a variety of peptide aldehydes (MG101, MG132 and MG115) which are inhibitors of protease activity, lactacystin which blocks proteasome activity by acylation of a key proteasome subunit and a group of boronic acid peptides including PS-341 are all extremely potent inhibitors of proteasome function [107]. PS-341 has shown promise as an adjunct to cancer chemotherapy by inhibiting activation of the NF-κB pathway. A variety of potential inhibitors of proteasome function may have a role inhibiting the NF-κB pathway.

Therapeutic Implications of Inhibiting the NF-κB Pathway

The evidence presented suggests that the NF-κB pathway plays a critical role in the pathogenesis of a number of disease states including rheumatoid arthritis, inflammatory bowel disease and atherosclerosis. A better understanding of the regulation of the NF-κB pathway in both normal and disease states may provide opportunities to better understand and treat these diseases. Furthermore NF-κB is an excellent target for new types of treatments to block the inflammatory response in instances where this process becomes chronic or dysregulated. Inhibition of the NF-κB pathway may also provide a useful target to enhance the efficacy of cancer therapy since dysregulated NF-κB activity may contribute to the onset or the progression of tumors. For example, blocking the NF-κB pathway may enhance stimuli-induced apoptosis such as seen following chemotherapy and radiation therapy. It may not be possible to block the NF-κB pathway for prolonged periods using general inhibitors of this pathway, such as proteasome inhibitors, since NF-κB plays an important role in the maintenance of host defense responses. However, specific inhibition of different components of the pathway such as IKK activity might reduce these potential side effects and result in a new class of anti-inflammatory and anti-cancer agents. Further studies to address the role of alterations in NF-κB regulation on human disease states may lead to the development of novel therapeutic strategies.

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